REMARKS

Claims 1-28 are pending. Claims 14-27 presently stand withdrawn from consideration as being directed to nonelected subject matter. Applicants have cancelled claim 15 without prejudice and added claims 29-44. Claims 1-14, 16-19, and 21-44 will therefore be pending upon entry of the proposed amendments and rejoinder of nonelected claims 14-19 and 21-27.

Applicants have deleted the phrase "and prodrug forms" from claim 1; and replaced the term "solvates" in claim 13 with "hydrates."

Applicants have amended claim 16 as follows:

- Applicants have rewritten claim 16 to depend from claim 1 instead of claim 15, now cancelled.
- Claim 16 as currently amended is now directed to methods for treatment of the disorders and medical conditions recited in the claim instead of methods for the prophylaxis or treatment of the recited disorders and medical conditions.
- Applicants have deleted "fibromyalgia;" "thrombotic illness including stroke;" "memory disorders;" "mood disorders;" "autism;" "depression with coexisting diabetes;" "sexual function disorders;" "sleep disorders;" "pain;" "Parkinson's disease;" "glaucoma including normal tension glaucoma;" "urinary incontinence including urinary incontinence with co-existing diabetes;" and "diabetic complications" from the listing of contemplated disorders and medical conditions.

As such, claim 16 as currently amended is directed to methods for treatment of a disorder or medical condition selected from angina; Raynaud's phenomenon; intermittent claudication; coronary or peripheral vasospasms; hypertension; schizophrenia; obsessive-compulsive disorder; attention deficit hyperactivity disorder (ADHD); anxiety disorders; depression disorders substance abuse; extrapyramidal symptoms; menopausal and post-menopausal hot flushes; premenstrual syndrome; bronchoconstriction disorders; or eating disorders.

Similarly, Applicants have rewritten claims 17 and 18 depend from claim 1 instead of claim 15, now cancelled. Claims 17 and 18 as currently amended are directed to methods for the treatment (but not prophylaxis) of Alzheimer's disease and a disorder or medical condition associated with neuroleptic drug therapy, respectively.

Claim 19 has been amended to depend from claim 16 instead of claim 15, now cancelled.

New claims 29-44 include the subject matter deleted from claim 16. More specifically, new claims 29-44 are directed to methods for the treatment (but not prophylaxis) of the disorders and medical conditions deleted from claim 16. The methods of new claims 29-44 include administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 1.

Finally, Applicants have amended the title as required by the Examiner.

No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-13 and 28 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. The Office has argued (Office Action, page 3):

> [T]he specification, while being enabling for production of the compounds following formula (I), pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers and N-oxides thereof, does not reasonably provide enablement for prodrug forms thereof.

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution, Applicants have deleted the term "prodrug forms" from claim 1. Applicants therefore respectfully request reconsideration and withdrawal of the rejection in view of the amendment to claim 1.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-13 and 28 are rejected under 35 U.S.C. § 112, first paragraph for allegedly being indefinite. The Office has argued: "[t]he term 'and prodrug forms thereof,' present as a limitation in claim 1, renders that claim indefinite in scope" (Office Action, page 8).

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution, Applicants have deleted the term "prodrug forms" from claim 1. Applicants therefore respectfully request reconsideration and withdrawal of the rejection in view of the amendment to claim 1.

Claim 13 is further rejected because "the phrase 'and solvates' lacks antecedent basis in claim 1" (Office Action, page 9). This rejection is moot in view of the amendment to claim 13.

Applicants submit that the foregoing amendments place claims 1-13 and 28 in condition for allowance. As such, Applicants respectfully request rejoinder and examination of withdrawn claims 14-19 and 21-27 as well as examination of new claims 29-44, which are within the purview of Group II of the present restriction requirement.

Office's Comments Regarding Withdrawn Claims 15-18

The Office has indicated that claims 15-18 in their previously presented form would be rejected under 35 U.S.C. § 112, first paragraph upon their rejoinder. According to the Office (Office Action, pages 11-12, italics and underlining in original; bolded emphasis added):

> In short, treatment of the following conditions and diseases is not enabled by the disclosure: fibromyalgia, thrombotic illness including stroke, memory disorders, mood disorders, autism, depressive disorders *including depression with coexisting diabetes* (though treatment of depressive disorders is enabled by the disclosure), sexual function disorders, sleep disorders, pain, Parkinson's disease, glaucoma including normal tension glaucoma, urinary incontinence including urinary incontinence with co-existing diabetes, and 'diabetic complications.' Prophylaxis of no condition or disease is enabled by the disclosure **because prophylaxis requires complete elimination of the disease or condition**.

Applicants wish to thank Examiner Tucker for the courtesy of providing the comments found on pages 10-13 of the Office Action.

Applicants respectfully disagree with the Office's assertion that claims 15-18 do not satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. However, to expedite prosecution, Applicants have canceled claim 15 and narrowed claims 16-18 to encompass methods for treatment of the recited disorders, but not methods for the prophylaxis of these disorders. That said, Applicants wish to address the bolded statement in the above-quoted passage from page 12 of the Office Action. Practicing the methods of claims 15-18 does not require "complete elimination of the disease or condition." There is nothing in the claims 15-18 that imposes such a narrow and absolute limitation on prophylaxis, nor is there anything in the Specification to support such an overly restrictive interpretation of prophylaxis. While a broad interpretation would encompass the embodiment pointed by the Office, it would also encompass other benchmarks, e.g., reducing the incidence of symptoms associated with a particular disease. In any event, the Office has provided no evidentiary basis for the statement "prophylaxis requires complete elimination of the disease or condition."

As will be discussed in more detail below, Applicants maintain that the Specification does indeed enable the disorders and medical conditions mentioned in the above-quoted passage from pages 11-12 of the Office Action. Applicants offer for the Examiner's consideration (1) experimental data showing the ability of one of the claimed compounds to lower intraocular pressure in monkeys; and (2) a Supplemental Information Disclosure Statement to disclose articles and patent documents that describe the involvement of 5-HT_{2A} in the aforementioned disorders and medical conditions. For purposes of clarification, the term "5-HT_{2A} receptor" refers to the receptor formerly named as the "5-HT_2" or "serotonin S_2" receptor.

Glaucoma

Glaucoma generally refers to disorders that can lead to damage to the optic nerve, which is the nerve that carries visual information from the eye to the brain. Damage to the optic nerve can result in vision loss and ultimately may progress to blindness. Most people with glaucoma have increased fluid pressure in the eye, a condition known as increased intraocular pressure (IOP).

1. Effect of the selective 5–HT2A antagonist 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-methyl-1-piperazinyl)-2(1*H*)-pyrazinone on the intraocular pressure in monkeys

The effect of two different topical doses of 1-[2-(2,4,5-trifluorophenoxy)ethyl]-3-(4-methyl-1-piperazinyl)-2(1*H*)-pyrazinone, which is described in Example 54 of the Specification ("Example 54"), on intraocular pressure (IOP) in ocular normotensive cynomolgus monkeys was determined.

Methods

Before administration of Example 54, baseline IOP was measured by Goldmann applanation tonometry in eight ocular normotensive cynomolgus monkeys, and a slit lamp examination (SLE) was performed under ketamine anesthesia. The animals were randomly divided in to two groups of four. Example 54, dissolved in phosphate buffer at pH 6.0 in

concentrations of 10mM (dose 1) and 50mM (dose 2), was administered to the right eyes of group 1 and the left eyes of group 2. Single doses of 10µl were administered once daily to the respective eyes and phosphate buffer at pH 6.0 (vehicle) was similarly administered to the contralateral eyes. There was a 1–week washout period between the last treatment with dose 1 and the first treatment with dose 2. On days 1 and 5, prior to the 1st and 5th dose, SLE was performed and a daily baseline IOP (BL) was measured. Following these doses, IOP was measured at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 hours. SLEs were done at 3 and 6 hours.

Results

On day 1, eyes treated with Example 54 showed an IOP decrease that was generally maintained for the duration of the 6 hour observation period; at 0.5 and 1.5 hours post treatment IOP significantly decreased from BL by 1.94±0.43 and 1.81±0.58 mmHg [mean±s.e.m.] ($p \leq 0.005$ and $p \leq 0.02$, respectively). Eyes treated with vehicle had no significant change in IOP. Following the 5th dose of Example 54, IOP decreased significantly, between 1.25 and 2.25 mmHg, at 1.5, 3, 4, 5 and 6 hours ($p \leq 0.05$) compared to BL. There were no significant post–treatment IOP changes in the vehicle–treated eyes. After 1 administration of Example 54 at dose 2, IOP decreased significantly by 1.31 to 2.06 mmHg when corrected for BL ($p \leq 0.05$), at 1.5, 2, 3, 4 and 6 hours, while vehicle–treated eyes showed no significant change. By day 5, Example 54–treated eyes showed significant changes of 1.63 to 2.88 mmHg, at 1, 1.5, 2, 3, 4 and 5 hours post–treatment ($p \leq 0.05$), while IOP in vehicle–treated eyes showed no significant change.

Conclusions

Example 54 treatments consistently produced a 1–3 mmHg reduction in mean IOP from BL pressures after 1 and 5 treatments at 10mM and 50mM doses. The two doses did not produce significantly different results, but dose 2 appears to have a more consistent and earlier effect.

2. Articles and patent documents that describe the involvement of 5-HT_{2A} in glaucoma

See, e.g.,

A) Costagliola, C. et al. "Effect of topical ketanserin administration on intraocular pressure". *Br. J. Ophthalmol.* **1993**, *77*, 344-348) (Costagliola) (emphasis added):

> Our results show that topical administration of ketanserin significantly reduces IOP in normotensive and hypertensive human eyes (Costagliola, p. 346). ...
>
> When injected into the anterior chamber, serotonin produces an increase both in IOP[22] and in the protein concentration.[23] Ketanserin has an inhibitory effect on the serotonin stimulated accumulation of inositol phosphates in the iris ciliary body[24]; on the contrary, the serotonin response is insensitive to atropine and prazosin, indicating that the serotonin effect is mediated by receptors that are distinct from α1 adrenergic and muscarinic cholinergic receptors. Thus, both experimental and clinical evidence confirms that the inhibitory action of ketanserin is not mediated by an antagonism of α adreno-receptors, **rather it is due to a specific blocking effect on the serotonin-2 receptor subtype** (Costagliola, p. 347). ...
>
> The lack of all these side effects together with its efficacy in lowering IOP puts ketanserin in a more favourable position when compared with β blocking agents in the treatment of glaucoma. Moreover, the analysis of the response curves suggests that two or three daily applications will manage IOP in glaucomatous patients (Costagliola, p. 347).

B) Mano, T. et al. "The effect of Anplag (Sarpogrelate HCl), new selective 5-HT_2 antagonist on intraocular pressure in rabbits". *Invest. Ophthalmol. Vis. Sci.* **1995**, *36*, S719; and Takenaka, H. et al. "The effect of Anplag (Sarpogrelate HCl), novel selective 5-HT_2 antagonist on intraocular pressure in glaucoma patients". *Invest. Ophthalmol. Vis. Sci.* **1995**, *36*, S734. These two abstracts describe the intraocular pressure lowering effect induced by the 5-HT_{2A} receptor antagonist sarpogrelate in rabbits and in glaucoma patients, respectively.

See also, e.g., EP 522226, EP695545 B1, and US 5538974.

With regard to normal tension glaucoma, see, e.g.:

A) Mermoud, A. et al. "Treatment of normal pressure glaucoma with a serotonin S2 receptor antagonist, naftidrofuryl (praxilen)" *Klin Monatsbl Augenheilkd.* **1991**,*198*(5):332-4. ("35 normal tension glaucoma patients were followed during 8 to 11 month. 12 patients received 2 x 200 mg/day Naftidrofuryl, a serotonine S2 receptor antagonist. As controles, another 23 patients were followed without treatment. The treated group, compared with the 23 non treated patients showed a significant increase in visual acuity ($p = 0.001$), a significant increase of the MS ($p = 0.03$), and a non significant decrease of the MD and CLV on the Octopus visual field (p, NS). The physiology and physiopathology of serotonine and S2 receptor antagonist are discussed." --see Abstract) .

B) Mermoud, A. et al. "Double-blind study in the treatment of normal tension glaucoma with naftidrofuryl" *Ophthalmologica.* **1990**;*201*(3):145-51 ("Mermoud, 1990"):

> Naftidrofuryl is an antiserotonin S2-specific agent, with the three following effects: (1) peripheral vasodilatation, (2) antiaggregation and (3) increase in cellular metabolic. These effects could be interesting in the management of the optic nerve ischemia of glaucomatous patients and especially of those with normal tension glaucoma. The administration of 2 x 200 mg/day of naftidrofuryl during 6 weeks to 12 patients with normal tension glaucoma has shown an improvement of the visual acuity and the visual field compared with a 6-week period of placebo administration, with a double-blind study method. It suggested that naftidrofuryl might be administered as a useful complement to conventional hypotensive therapy, since it acts positively on the glaucomatous optic nerve damage (Mermoud, 1990, Abstract). ...
>
> Antiserotonin S_2 can be a useful complement to conventional hypotensive therapy in glaucoma and especially in low tension glaucoma (Mermoud, 1990, page 150).

Thus, contrary to the Office's assertions on page 12 of the Office Action, treatment of glaucoma with a $5HT_{2A}$ receptor antagonist was indeed "a viable treatment option" (Office Action, page 12) as of Applicants' filing date.

Urinary incontinence including urinary incontinence with co-existing diabetes

See, e.g.,

A) Saxena, P.R. et al. "Excitatory 5-hydroxytryptamine receptors in the cat urinary bladder are of the M- and 5-HT2-type" *J. Autonom. Pharmacol.* **1985**, *5*, 101-107 ("These results clearly show that the early and late phases of the cat urinary bladder contraction elicited by 5-HT are mediated by M and 5-HT_2 receptors, respectively" --see Abstract).

B) Kodama, M. et al. "Influence of 5-hydroxytryptamine and the effects of a new serotonin receptor antagonist (sarpogrelate) on detrusor smooth muscle of streptozotocin-induced diabetes mellitus in the rat." *Int. J. Urol.* **2000**, *7*, 231-235 (Kodama):

> These results suggest that the increased contractile response to 5-HT in diabetic rats' bladder is related to smooth muscle hypertrophy and/or hyperplasia and indicate that this effect is mediated by activation of 5-HT2A receptors (Kodama, Abstract). ...
>
> Sarpogrelate, which we used as a 5-HT2A antagonist, is 100 times more potent than ketanserin in terms of 5-HT2A blocking activity.[17] Sarpogrelate hydrochloride is therefore considered a selective 5-HT2A antagonist. Our results indicated that serotonin-induced contraction of the rat bladder is mediated by activation 5-HT2A receptors (Fig.2). Given that serotonin is an important mediator of bladder contractility, 5-HT2A receptor antagonists may be useful in the management of bladder overactivity (Kodama, page 234).

C) Sugimoto, S. et al. "Characteristics of 5-HT2A receptors in the bladder muscle of diabetic rats" *Nihon Univ. J. Med.* **2001**, *43*, 141-152 (Sugimoto):

> 5-HT produces a reversible and dose-dependent contraction of the urinary bladder in intact animals such as rats,[9,10)] cats,[20)] dogs,[6)] pigs and humans,[7)] via 5-HT_2 receptors as a direct action. ... 5-HT contracts the intact bladder smooth muscle via the 5-HT_{2A} receptors, ...(Sugimota, page 148). ...
>
> Our results clearly demonstrated that the affinity for 5-HT_{2A} receptors in the rat bladder smooth muscle was significantly increased in diabetes mellitus. ... In this experimental study, we have shown that an increased affinity for 5-HT2A receptors in diabetic rats might be associated with the complex pathophysiology of diabetic cystopathy (Sugimota, page 150).

D) Kim H.J. et al. "Acute effects of serotonin on rat bladder contractility" *Urol. Int.* **2002**, *68*, 44-48 ("Because the 5-HT_2 antagonist blocked the effect of serotonin-induced bladder contractions and the stimulation of the adrenoreceptors, the 5-HT_2 antagonist seems to improve lower urinary tract symptoms" --see Abstract).

E) Takimoto, Y. et al. "The effect of 5-HT2 antagonist for urinary frequency symptom on diabetes mellitus patients" *Jpn. J. Urol.* **1999**, *90*, 731-740 ("It is believed that reaction in the detrusor muscle with hyperreflexia of diabetes mellitus patients can reach 5-HT, and its reaction is belived [*sic.*, believed] to reach the 5-HT 2 receptor. This paper is a first clinical report of making use of 5-HT 2 antogonist as hyperactive detrusor on diabetes mellitus patients" --see Abstract).

See also, e.g., Cohen, M.L. "Canine, but not rat bladder, contracts to serotonin via activation of 5-HT2 receptors" *J. Urol.* **1990**, *143*, 1037-1040; Yoshida, A. et al. "5-Hydroxytryptamine receptors, especially the 5-HT4 receptor, in guinea pig urinary bladder" *Jpn. J. Pharmacol.* **2002**, *89*, 349-355; Tammela, T.L.J. et al. "Temporal changes in micturition and bladder contractility after sucrose diuresis and streptozotocin-induced diabetes mellitus in rats" *J. Urol.* **1995**, *153*, 2014-2021; Ichiyanagi, N. et al. "Changed responsiveness of the detrusor in rabbits with alloxan induced hyperglycemia: possible role of 5-hydroxytryptamine for diabetic bladder dysfunction" *J. Urol.* **2002**, *168*, 303-307; Menendez, V. et al. "Urodynamic evaluation in simultaneous insulin-dependent diabetes mellitus and end stage renal disease" *J. Urol.* **1996**, *155*, 2001-2004; and Kaplan, S.A. et al. "Urodynamic findings in patients with diabetic cystopathy" *J. Urol.* **1995**, *153*, 342-344.

Depression with co-existing diabetes

See, e.g.,

A) Sumiyoshi, T. et al. "The effect of streptozotocin-induced diabetes on dopamine2, serotonin1A and serotonin2A receptors in the rat brain". *Neuropsychopharmacology* **1997**, *16*, 183-190 (Sumiyoshi):

> The affinity constants for D_2, 5-HT_{1A}, and 5-HT_{2A} receptors were not affected by any treatment. There results suggest that diabetic state may affect brain serotonergic activity via an increase in the density of 5-HT_{2A} receptors. This may indicate an increased vulnerability to major depression in patients with diabetes (Sumiyoshi, Abstract). ...
>
> In conclusion, the present study demonstrated that STZ-induced DM increased the density of 5-HT_{2A} receptors, but did not affect D_2 or 5-HT_{1A} receptor densities in the rat brain. The increase in the density of D_2 receptors by chronic HPD treatment was abolished in STZ-induced DM rat. The 5-HT_{2A} receptor unregulation and the inability of D_2 receptors to respond to chronic neuroleptic treatment may be further evidence of altered DA and 5-HT neurotransmission in the diabetic state and suggest a possible basis for the vulnerability of patients with DM to develop tardive dyskinesia or major depression (Sumiyoshi, page 189).

B) Jackson J. et al. "Enhancement of [*m-methoxy* 3H]MDL100907 binding to $5HT_{2A}$ receptors in cerebral cortex and brain stem of streptozotocin induced diabetic rats". Mol. Cell. Biochem. 1999, 199, 81-85 (Jackson):

> Thus, from our study we conclude that STZ-induced diabetes causes an increase in affinity of cerebral cortex 5-HT_{2A} receptors without any change in the number of receptors. The brain stem 5-HT_{2A} receptors are upregulated accompanied by the appearance of a low affinity site which was reversed to control by insulin treatment. The enhanced 5-HT_{2A} receptor binding observed in brain regions can mediate an increased sympathetic nerve discharge in a similar way as central 5-HT_{1A} receptors leading to inhibition of insulin release from pancreas and can also mediate diabetes induced depression (Jackson, page 85).

See also, e.g., Dursun, S.M. et al. "An exploratory approach to the serotonergic hypothesis of depression: bridging the synaptic gap". *Med. Hypotheses* **2001**, *56*, 235-43.

Memory Disorders

See, e.g.:

A) Nabeshima, T. et al. "Effect of naftidrofuryl oxalate on 5-HT_2 receptors in mouse brain: evaluation based on quantitative autoradiography and head-twitch response". Eur. J. Pharmacol. 1992, 223, 109-115 (Nabeshima):

> Although the effect of LS-121 on 5-HT_2 receptors was weaker than that of methysergide or ritaserin, LS-121 had a moderate affinity for 5-HT_2 receptors, indicating that LS-121 may be effective in various forms of cognitive disturbance related to the 5-HT neuronal system.
>
> In conclusion, LS-121 significantly inhibits [3H] ketanserin binding to 5-HT_2 receptors, with a potency similar to that of methysergide and ritanserin. These findings suggest, therefore, that LS-121 inhibits head-twitch responses by blocking 5-HT_2 receptors (Nabeshima, page 114).

B) Weinberger, D.R. et al. "Cognitive function in schizophrenia". *Int. Clin. Psychopharmacol.* **1997** Sep;12 Suppl 4:S29-36 (Weinberger). This article discusses that cognitive function can be markedly impaired in patients with schizophrenia, and that 5-HT_{2A} antagonists may improve the cognitive function in patients with schizophrenia ("The development of sophisticated, computer-delivered maze tasks has shown that newer antipsychotics, such as clozapine and risperidone, differ from conventional neuroleptics in their effects on cognitive function. The prospects, therefore, are that patients treated with drugs having 5-HT_{2A} blocking activity will have better cognitive function and will be better able to function in life's roles than will patients treated with conventional neuroleptics" --see Abstract).

See also, WO 2001089498 discloses use of the 5-HT_{2A} antagonist M-100907 for treatment of symptoms of, e.g., dimentia. In Example #5 of WO 2001089498, M-100907 was shown to antagonize scopolamine-stimulated locomotion in rats. Scopolamine-induced hyperlocomotion in the rat has sometimes been used as a model of behavioral disturbances related to cholinergic deficiency states such as Alzheimer's disease.

Sleep Disorders

See, e.g.:

A) Radulovacki, M., et al. *Research Communications in Biological Psychology and Psychiatry* **2001**, *26*(1 & 2), 3-14 (Radulovacki):

> The major finding was that ketanserin significantly reduced the post-sigh apnea frequency in a dose-dependent fashion during both NREM and REM sleep and suppressed spontaneous apneas only with the highest dose in both sleep stages (Figures 2 and 3) (Radulovacki, page 9). …
>
> In conclusion, our data implicate activity of endogenous serotonin at 5-HT_2 receptors in the genesis of sleep-related apnea. … Still, the present data provide a rationale for further evaluation of the pharmacotherapeutic potential of 5-HT_2 receptor antagonists in the treatment of sleep related breathing disorders (Radulovacki, page 12).

B) See also, e.g., WO 00/12090, which discloses the use of the 5-HT_{2A} antagonist R(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (M-100907, also named MDL-100907) for the treatment of sleep disorders such as insomnia and obstructive sleep apnea; US 6,143,792, which discloses that the 5-HT_{2A} antagonist (1Z,2E)-1-(2-fluorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one-O-(2-dimethylaminoethyl)oxime (SR 46349 B) is "efficacious" in the treatment of the sleep apnea syndrome (col. 2, lines 47-51); and Viola, A.U., et al. "Ritanserin, a serotonin-2 receptor antagonist, improves ultradian sleep rhythmicity in young poor sleepers" *Clinical Neurophysiology* **2002**, *113*(3), 429-434.

Autism

See, e.g.:

US 6,358,977 discloses biological data (a hypoglutamatergic mouse model) showing that MDL-100907 was able to alleviate the deficient habituation (recorded as reduced hyperactivity) induced by the glutamate antagonist MK-801 (dizocilpine) without interfering with normal behaviour of the animals; evidence that illustrates the anti-autistic effects of the 5-HT_{2A} antagonist, MDL-100907.

Diabetic Complications

Diabetic Retinopathy; see, e.g.:

A) Pietraszek, M.H. et al. "Blood serotonergic mechanisms in type 2 (non-insulin-dependent) diabetes mellitus". Thromb. Res. 1992, 66, 765-774 (Pietraszek, 1992):

> Our preliminary communication has shown that enhanced platelet response to serotonin in Type 2 diabetes was related to vascular complication such as retinopathy (Pietraszek, 1992, page 766). ...
>
> All diabetic patients had significantly higher level of plasma 5HT in comparison with normal persons ($p<0.001$). Those patients with clinical evidence of simple or proliferative retinopathy had higher levels of plasma serotonin than those patients without retinopathy and these differences reached statistical significance ($p<0.05$) (Pietraszek, 1992, page 768-9). ...
>
> Serotonin itself is a very weak activator of human platelets but in some pathological conditions the aggregation of platelets with their degranulation have been shown (14). ... In conclusion, in the present study we have shown that Type 2 diabetes mellitus is associated with many abnormalities in blood serotonergic system. Our results indicate that vascular complications in diabetic patients may be mediated in part by serotonin (Pietraszek, 1992, page 773).

See also, e.g., Pietraszek, M.H. et al. "Enhanced platelet response to serotonin in diabetes mellitus in relationship to vascular complications". *Thromb. Haemost.* **1991**, *65*, 985.

B) Pietraszek, M.H. et al. "The effect of MCI-9042 on serotonin-induced platelet aggregation in type 2 diabetes mellitus". *Thromb. Res.* **1993**, *70*, 131-138 (Pietraszek, 1993):

> MCI-9042, a potent inhibitor of 5HT2 receptor, was used to examine its effects on serotonin induced-aggregation of platelets obtained from patients with type 2 diabetes mellitus (DM). The extent of platelet aggregation induced by serotonin increased in DM patients without retinopathy, but the increase was further significant in DM patients with retinopathy. MCI-9042 dose dependently inhibited platelet aggregation induced by serotonin and collagen. These results suggest that serotonin which may be released from platelets of DM patients may activate platelets together with collagen exposed on atherosclerotic endothelium and that MCI-9042 may be inhibitory to enhanced platelet aggregability under these conditions (Pietraszek, 1993, Abstract).

See also, e.g., Malyszko, J. et al. "Daily variations of platelet aggregation in relation to blood and plasma serotonin in diabetes". Thrombosis Res. 1994, 75, 569-576 ("An enhanced response of diabetic platelets to 5-HT together with elevated plasma 5-HT levels may contribute, at least partly, to the pathogenesis of diabetic vasculopathy and $5HT_2$ receptor blockers may be of value in DM patients" --see Abstract).

Diabetic Nephropathy; see e.g.:

A) Ogawa, S. et al. "The 5-HT_2 receptor antagonist sarpogrelate reduces urinary and plasma levels of thromboxane A_2 and urinary albumin excretion in non-insulin-dependent diabetes mellitus patients". *Clin. Exp. Pharmacol. Physiol.* **1999**, *26*, 461-464 ("In conclusion, microalbumia was improved by treatment with the 5-HT_2 receptor antagonist sarpogrelate independent of latent vasculopathy. Blockade of 5-HT_2 receptors is suggested to be beneficial for the treatment of nephropathy in NIDDM patients. It is possible that the inhibition of TXA_2 biosynthesis is involved in the therapeutic effect of 5-HT_2 receptor antagonists" --see Abstract).

B) Kobori, S. et al. "Effect of 5-hydroxytryptamine2A receptor antagonist on the development of diabetic nephropathy in early stage". *Int. Congr. Ser.* **2000**, 283-286 ("It is suggested that the development of diabetic nephropathy in early stage may be inhibited by 5-HT2A receptor antagonist" --see Abstract).

Diabetic Neuropathy; see, e.g.:

A) Hotta, N. et al. "Effects of the 5-HT_{2A} receptor antagonist sarpogrelate in diabetic patients with complications: A pilot study". Clinical Drug Investigation 1999, 18(3), 199-207 ("We administered the 5-HT_{2A} receptor antagonist sarpogrelate to patients with diabetes mellitus and associated circulatory disorders in the lower limbs and found it to be useful not only for lower limb circulatory disorders but also for neuropathy" --see page 206).

See also, e.g., Ishimura, E. et al. "Therapeutic effect of sarpogrelate, a new 5-hydroxytryptamine receptor 2A antagonist, on diabetic nephropathy and neuropathy". *Nephron*

1997, *76*, 227-229; and Takei, I. et al. "Effects of the 5-HT_2 receptor antagonist sarpogrelate on diabetic vascular disease". *Diabetes Res.* **1999**, *34*, 239-246.

B) Martinez-De Jesus, F.R. et al. "Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers". *Arch. Med. Res.* **1997**, *28*, 95-99 ("In conclusion, topical ketanserin significantly accelerated wound healing in diabetic neurotrophic foot ulcers when applied as part of a comprehensive healing program" --see Abstract).

See also, e.g., Apelqvist, J. et al. "Ketanserin in the treatment of diabetic foot ulcer with severe peripheral vascular disease." *International Angiology* **1990**, *9*, 120-124.

Sexual Dysfunction

Sexual dysfunction often occurs in patients treated with selective serotonin reuptake inhibitors (SSRI). 5-HT_{2A} antagonists have been shown to reverse SSRI-induced dysfunction (Schechter et al. 1999 Curr Opin in CPNS Invest Drugs 1:432), suggesting the such antagonists could be useful for the treatment of certain sexual dysfunctions.

Fibromylagia

Certain 5-HT2A receptor antagonists have been shown to be useful for the treatment of fibromylagia. For example, ketanserin, a 5-HT2A antagonist, has been tested in patients suffering from fibromylagia. Patients treated with ketanserin experienced a significant reduction in pain. Moreover, the painfulness of "tender points" decreased markedly in the treated paients. The treated patients also experienced a significant improvement in the quality of sleep, the feeling of being rested after sleep, and physiological well-being in the evening (Stratz et al. Zeitschrift fur Rheumatologie 1991 50:21. Based on another study of ketanserin in patients suffering from fibromylagia, Hemmeter et al. concluded that "5-HT2-receptor-antagonist may be a new strategy for the common treatment of sleep disturbance and the pain syndrome which needs to be evaluated in further studies" (Schweiz Med Wochenschr 125:2391, 1995).

Neuroleptic Drug Therapy

Several studies suggest that 5-HT2A antagonists can lower the risk of neuroleptic-induced extrapyramidal symptoms in patients suffering from schizophrenia (Leysent et al. 1997 Curr Pharmaceutical Design 3:367). For example, MDL-100907, a highly selective 5-HT2A receptor antagonist, has antipsychotic properties with low EPS liability (Sorbera et al. 1998 Drugs of the Future 23:955). In addition, when administered with haloperidol, ritanserin, a 5-HT2A receptor antagonist, improved negative symptoms in schizophrenia patients and reduced extrapyramidal symptoms induced by haloperidols blockage of dopamine receptors.

Thrombotic illness

Studies in animal models have shown that a 5-HT2A receptor antagonist can be effective in the treatment of thrombotic diseases. Serotonin (5-HT) is released from activated and aggregated platelets at the site of vascular injury. Studies of sarpogrelate (MCI-9041), a selective 5-HT2A receptor antagonist, have shown that it exhibits anti-thrombotic effects and have lead researchers to conclude that it is "an effective agent to treat thrombotic diseases" (Hara et al. 1991 Thrombosis and Haemostasis 66:484). In one study, sarpogrelate was found to be more effective than ticlopidine hydrochloride in the treatment of certain aspects of chronic arterial occlusive disease (Furukawa et al. 1991 J Clin Ther Med 7:1747). Moreover, studies on AT-1015, a different 5-HT2A receptor antagonist, led to the suggestion that "AT-1015 is a potent and long-acting oral antithrombotic agent" in a model of arterial thrombosis (Kihara et al. 2001 Eur J Pharm 433:157).

Pain

There is considerable evidence, including in patients, that 5-HT2A receptor antagonists can be used to treat pain. Abbott et al. (Neurpharmacology 35:99, 1996) used various selective 5-HT receptor antagonists to investigate the 5-HT receptor subtype that mediates the synergistic effect of serotonin and other inflammatory mediators. The authors conclude that "5-HT2A antagonists may be effective peripherally acting analgesic agents and/or analgesic adjuncts" in

situations where 5-HT release contributes to the generation of pain. Another study concluded that the 5-HT2A receptor subtype is involved in 5-HT-induced hyperplasia in acute injury and inflammation in a rat model (Tokunaga et al. 1998 Pain 76:349). Sarpogrelate, a selective 5-HT2A receptor antagonist, was found to reduce pain a reduce bone atrophy in patients suffering from complex regional pain syndrome (Otake et al. 1998 Can J Anaesth 45:831). Finally, Obata et al. (Eur J. Pharmacol. 404:95, 2000) reported that sarpogrelate exhibits antinociceptive effects and that "local application of a selective 5-HT2A receptor antagonist may be effective to treat pain provoked by 5-HT release from platelets, which commonly occurs with injury and inflammation.

Stroke

Several antagonists of 5-HT2 are in various stage of experimental or clinical trials for the treatment of stroke and some positive results have been observed with 5-HT2A antagonists. The effect of 5-HT and a 5-HT2A antagonist, ketanserin, on collateral and normal blood flow in dogs following cerebral artery occlusion was studied by Scott et al. (Surgical Form 47:561, 1996). The authors found that the decrease in aortic and cerebral pressure usually seen with 5-HT administration was attenuated by ketanserin. The authors concluded that "5-HT receptor antagonists may prevent the progression of ischemic damage following occlusion of a cerebral artery an thus play a role in stroke management. In another study, ketaserin was found to significantly reduce remote hemodynamic consequences of thrombotic infarction (Dietrich et al. 1989 J Cerebral Blood Flow and Metabolism 9:812).

CONCLUSION

Applicants submit that all claims are in condition for allowance.

Enclosed is a $1,020 check for the Three Month Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 13425-122001.

Respectfully submitted,

Date: June 27, 2006

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